

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 June 2001 (14.06.2001)

PCT

(10) International Publication Number
WO 01/42209 A1

(51) International Patent Classification⁷: C07D 207/34, A61K 31/40

(21) International Application Number: PCT/IB00/01797

(22) International Filing Date: 5 December 2000 (05.12.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P-9900271 10 December 1999 (10.12.1999) SI

(71) Applicant (*for all designated States except US*): LEK
PHARMACEUTICAL AND CHEMICAL COMPANY
D.D. [SI/SI]; Verovškova 57, 1526 Ljubljana (SI).

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): PFLAUM, Zlatko
[SI/SI]; Češminova 23, 1230 Domžale (SI).

(81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— With international search report.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PREPARATION OF AMORPHOUS ATORVASTATIN

(57) Abstract: Atorvastatin, the substance known by the chemical name [R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid hemi calcium salt, is readily available in one of its crystalline forms as it is known from the prior art. The present invention relates to a novel process for preparing atorvastatin in an amorphous form by precipitating the atorvastatin using a solvent of a second type from a solution of atorvastatin which is provided with a solvent of a first type. This process is useful for the conversion of atorvastatin in a crystalline form into atorvastatin in an amorphous form.



WO 01/42209 A1

EXPRESS MAIL NO. EV545395338US
DOCKET NO. PC25264A

- 1 -

**Process for the Preparation of Amorphous
Atorvastatin**

The present invention relates to a novel process for the preparation of atorvastatin in an amorphous form.

- 5 Atorvastatin, the substance known by the chemical name
[R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-5-
(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-
1H-pyrrole-1-heptanoic acid hemi calcium salt is known as
HMG-CoA reductase inhibitor and is used as an
10 antihypercholesterolemic agent. Processes for the
preparation of atorvastatin and key intermediates are
disclosed in the United States Patent Numbers: 5,003,080;
5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251;
5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,342,952;
15 and 5,397,792. Atorvastatin is usually prepared as its
calcium salt since it enables atorvastatin to be
conveniently formulated in the pharmaceutical
formulations, for example, in tablets, capsules, powders
and the like for oral administration.
- 20 Atorvastatin can exist in an amorphous form or in one of
the crystalline forms (Form I, Form II, Form III and
Form IV), which are disclosed in the PCT patent
applications WO-A-97/3958 and WO-A-97/3959. It is known
that the amorphous forms in a number of pharmaceutical
25 substances exhibit different dissolution characteristics
and bioavailability patterns compared to the crystalline
forms (Konno T., *Chem Pharm Bull.*, 1990,38: 2003-2007).
For some therapeutic indications the bioavailability is
one of the key parameters determining the form of the
30 substance to be used in a pharmaceutical formulation.
Since processes for the crystallization and the

- 2 -

preparation, respectively, of the amorphous substance are sometimes difficult to be performed, and as a product afford amorphous-crystalline mixtures, that is, a crystalline form instead of an amorphous form, there is a constant need for processes which enable the preparing of atorvastatin in an amorphous form without simultaneous formation of crystalline forms, or which will enable the conversion of the crystalline forms into the amorphous form.

Atorvastatin is the substance which is very slightly water-soluble, and it has been found that the crystalline forms are less readily soluble than the amorphous form which may cause problems in the bioavailability of atorvastatin in the body. It has been found that the production of amorphous atorvastatin according to the previously disclosed processes was not consistently reproducible, therefore the process has been developed for converting the crystalline forms of atorvastatin (formed in the synthesis of atorvastatin) to the amorphous form. The process is described in the PCT patent application WO-A-97/3960 and comprises dissolving the crystalline form of atorvastatin in a non-hydroxylic solvent and after removal of the solvent affords amorphous atorvastatin. The preferred non-hydroxylic solvent is selected from the group consisting of tetrahydrofuran, and mixtures of tetrahydrofuran and toluene. The disadvantage of the above process is primarily the use of non-nature-friendly solvents. Furthermore, even after extensive and strict drying measures, the amorphous atorvastatin product still contains amounts of the non-hydroxylic solvent.

It is an object of the present invention to provide an improved process for the preparation of atorvastatin in a

- 3 -

more amorphous state compared to the above-mentioned processes of the prior art.

This and further objects are accomplished by the present invention.

- 5 The object of the present invention is achieved by a process for the preparation of atorvastatin in an amorphous form, which comprises:
- 10 a) providing a solution of atorvastatin in one or more solvents of a first type such that atorvastatin is freely soluble;
 - b) providing a mixture of said atorvastatin solution with one or more solvents of a second type, in which atorvastatin is insoluble or very slightly soluble, such that atorvastatin precipitates;
 - 15 c) separating the precipitate formed in step (b) from the mixture of solvents.

Further objects can be achieved by preferred embodiments as set forth in the claims being dependent from claim 1.

In the following, the drawings will be briefly described.

Figure 1: Diffractogram of amorphous atorvastatin prepared by a process according to the present invention.

Figure 2: Diffractogram of crystalline atorvastatin (Form I crystals).

- 20 X-ray diffraction measurements were carried out with an X-ray powder diffractometer (Siemens D-5000) using a Cu-K α light source ($\lambda=1.5406$ Å, 20 mA) within 2 to 37° 2 θ

- 4 -

range with a 0.035° 2θ step and an integration time of 1 second/step. Variable slits were adjusted to 20 mm sample illumination, and entrance slit to 0.6 mm.

The features of the present invention will become more
5 apparent from the following description of the inventive concept and the description of the preferred embodiments.

In the inventor's investigations, it was found that by means of combined steps of (i) providing a solution of atorvastatin and (ii) precipitating atorvastatin in
10 respectively appropriate solvent media, amorphous atorvastatin can be obtained in an efficient manner at a high yield and in pure form with ease and with solvents which are cheap and environmentally less critical and less harmful to health than those required according to
15 WO-A-97/3960.

In the first step of the process according to the present invention, a solution of atorvastatin is provided. Preferably, the solution used is obtained in the last step of the preparation of atorvastatin, or is obtained
20 by dissolving crystalline atorvastatin or a mixture of crystalline and/or polycrystalline and amorphous atorvastatin, which is usually obtained by the preparation of solid atorvastatin, in one or more solvents of the first type such that atorvastatin is
25 freely soluble (step a). The expression "*freely soluble*" means that atorvastatin can be fully dissolved in one or more solvents of the first type, i.e. without any remaining solid. More specifically, the amount of first type solvent required for solving 1 part of atorvastatin
30 may be in the range of less than 1 part to 30 parts, and more preferably less than 1 part to 10 parts. One or more

- 5 -

solvents means one solvent species or a mixture of solvent species of the first type.

For preferably achieving a fast precipitating of amorphous atorvastatin in step (b), the concentration of the
5 solution of atorvastatin containing one or more solvents of the first type is preferably adjusted to a range of 0.1 to 150 g/l, and more preferably 4 to 100 g/l.

In the second step (step b), a mixture of the above-mentioned atorvastatin solution with one or more solvents
10 of the second type, in which atorvastatin is insoluble or very slightly soluble, is provided. The mixing step is carried out that, finally, atorvastatin precipitates. More specifically, the terms "insoluble" and "very slightly soluble" may be understood to mean that the amount of
15 second type solvent required for solving 1 part of atorvastatin at room temperature and atmospheric pressure is in the range of 1.000 parts to 10.000 parts or more, and more preferably of 8.000 parts to 10.000 parts or more. One or more solvents means one solvent species or a
20 mixture of solvent species of the second type.

The mixing in step (b) may be accomplished in two different embodiments. In a first embodiment, the mixture is provided by adding one or more solvents of the second type into the atorvastatin solution obtained in step (a).
25 In a second, preferred embodiment, the mixture is provided by adding the atorvastatin solution of step (a) into one or more solvents of the second type. Both embodiments result in the precipitation of amorphous atorvastatin in a pure form.

30 In step (c) of the process according to the present invention, the precipitate of amorphous atorvastatin

- 6 -

formed in step (b) is separated from the mixture of solvents used. The separation of atorvastatin may be accomplished by decanting, filtrating and similar processing methods for separating solids from liquids
5 known from the prior art, or any combination of these separation methods.

Then, the amorphous atorvastatin product obtained may preferably be dried in a further step (d).

Step (a) of the process according to the present
10 invention may be modified such that firstly either a solution of atorvastatin is provided in one or more solvents of the first type or crystalline atorvastatin is dissolved in one or more solvents of the first type, and secondly a mixture of this solution is provided with one
15 or more solvents of the second type with the proviso that atorvastatin is still soluble, i.e. does not yet precipitate, in this mixture of solvents.

Moreover, the atorvastatin solution may advantageously concentrated before the second type solvent is added to
20 obtain a more concentrated solution of atorvastatin, which is useful for requiring only a small amount of the one or more solvents of the second type and for obtaining atorvastatin at a high yield by adding.

In a preferred embodiment for the processing of step (b),
25 a first mixture is provided by adding one or more solvents of the second type into the solution of step (a) such that atorvastatin is still soluble, i.e. does not yet precipitate, followed by adding additional amounts of one or more solvents of the second type such that
30 atorvastatin precipitates. To decrease the tendency of crystallization of atorvastatin, a fast addition in the

- 7 -

second step (b) is preferably carried out, e.g. during continuous stirring of the solution.

The one or more solvents of the first type used in the process of the present invention are selected from the group of solvents, in which atorvastatin is soluble or good soluble. Preferred examples of solvents of the first type are polar solvents such as low molecular alcohols, e.g. methanol and ethanol, or polar aprotic solvents such as ketones, e.g. acetone, ethyl methyl ketone, diethyl ketone, diisopropyl ketone, and the like, esters, e.g. ethyl acetate, n-butyl acetate, isobutyl acetate, and the like, chlorinated solvents, e.g. chloroform, methylene chloride, and the like, dimethyl formamide, dimethyl sulfoxide, tetrahydrofuran or the like. Particularly preferred solvents of the first type are selected from the group of solvents consisting of methanol, ethanol and acetone, which can easily be removed in the drying step and are less harmful or environmentally hazardous than the conventionally used solvents.

The one or more solvents of the second type used in the process of the present invention are selected from the group of solvents, in which atorvastatin is insoluble or very slightly soluble. The low solubility of atorvastatin in this solvent is preferably at most 1 part of atorvastatin / from 1.000 to 10.000 or more parts of second type solvent and more preferably at most 1 part of atorvastatin / from 8.000 to 10.000 or more parts of second type solvent. Preferred examples of solvents of the second type are solvents such as ethers, aliphatic compounds or the like. Particularly preferred solvents of the second type are selected from the group of solvents consisting of diethyl ether, diisopropyl ether, pentane, hexane, and the like, in which atorvastatin is very

- 8 -

slightly soluble or insoluble, but which can easily be removed in the drying step and which are less harmful or environmentally hazardous than the conventionally used solvents.

- 5 For preferably achieving a suitable precipitation, it is preferred that the total amount of the one or more solvents of the second type added to the solution of atorvastatin during the whole process of the present invention is at least 4 times higher, more preferably 5 to
10 12 times higher, than the total amount of the solvents of the first type added during the whole process. With such an excess of the one or more solvents of the second type over the one or more solvents of the first type the solubility of atorvastatin in the mixture of solvents is
15 low enough that the tendency of atorvastatin to crystallize is reduced and the yield of amorphous atorvastatin is excellent.

In view of this process according to the present invention, it is possible to prepare atorvastatin
20 essentially, and more advantageously completely in an amorphous state.

The present invention is illustrated but in no way limited by the following examples.

- 9 -

EXAMPLESExample 1

1.5 g of atorvastatin (crystalline Form I) were dissolved in 37.5 ml of methanol, concentrated to 10 ml on a rotary evaporator and to this solution were added 100 ml of ether. The formed precipitate was filtered and dried on a rotary evaporator (50°C. 100 mbar, 24 h). Yield: 1.3 g of the colourless precipitate of amorphous atorvastatin.

Example 2

1.5 g of atorvastatin (crystalline Form I) were dissolved in 300 ml of ethanol, concentrated to 30 ml on a rotary evaporator and to this solution were added 300 ml of ether. The formed precipitate was filtered and dried on a rotary evaporator (50°C. 100 mbar, 24 h). Yield: 1.3 g of the colourless precipitate of amorphous atorvastatin.

Example 3

1.5 g of atorvastatin (crystalline Form I) were dissolved in 136 ml of acetone, concentrated to 30 ml on a rotary evaporator and to this solution were added 300 ml of ether. The formed precipitate was filtered and dried on a rotary evaporator (50°C. 100 mbar, 24 h). Yield: 1.3 g of the colourless precipitate of amorphous atorvastatin.

Example 4

10 g of atorvastatin (crystalline Form I) were dissolved in 130 ml of methanol, concentrated to 30 ml on a rotary evaporator and to this solution were added 30 ml of ether. The resulting mixture was added to 1.300 ml of ether while stirring. The formed precipitate was filtered

- 10 -

and dried on a rotary evaporator (50°C, 100 mbar, 24 h).
Yield: 8.8 g of the colourless precipitate of amorphous
atorvastatin, however the obtained amorphous atorvastatin
had ca. 110% higher content than the starting crystalline
5 substance.

Example 5

90 g of atorvastatin (crystalline Form I) were dissolved
in 1 litre of methanol, filtered and concentrated to
300 ml on a rotary evaporator. To this solution were
10 added 500 ml of ether and while stirring it was added to
2.5 litres of ether. The formed precipitate was filtered
and dried on a rotary evaporator (50°C, 100 mbar, 24 h).
Yield: 87 g of the colourless precipitate of amorphous
atorvastatin.

15

Atorvastatin, the substance known by the chemical name
[R-(R*,R*)]-2-(4-fluorophenyl)- β , δ -dihydroxy-
5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-
1H-pyrrole-1-heptanoic acid hemi calcium salt, is readily
20 available in one of its crystalline forms as it is known
from the prior art.

The present invention relates to a novel process for
preparing atorvastatin in an amorphous form by
precipitating the atorvastatin using a solvent of a
25 second type from a solution of atorvastatin which is
provided with a solvent of a first type. This process is
useful for the conversion of atorvastatin in a
crystalline form into atorvastatin in an amorphous form.

- 11 -

Claims

1. A process for the preparation of atorvastatin in an amorphous form, which comprises:
 - 5 a) providing a solution of atorvastatin in one or more solvents of a first type such that atorvastatin is freely soluble;
 - b) providing a mixture of said atorvastatin solution with one or more solvents of a second type, in which atorvastatin is insoluble or very slightly
10 soluble, such that atorvastatin precipitates;
 - c) separating the precipitate formed in step (b) from the mixture of solvents.
2. A process according to claim 1, further comprising:
 - d) drying the amorphous product obtained.
- 15 3. A process according to claims 1 or 2, wherein said mixture in step (b) is provided by adding one or more solvents of the second type into the atorvastatin solution.
- 20 4. A process according to claims 1 or 2, wherein the mixture in step (b) is provided by adding the atorvastatin solution into one or more solvents of the second type.
5. A process according to any one of the preceding claims, wherein step (a) comprises the two steps:
 - 25 i) providing a solution of atorvastatin in one or more solvents of the first type, and
 - ii) providing a mixture by adding one or more solvents of the second type into said solution of

- 12 -

atorvastatin such that atorvastatin is still soluble in said mixture of solvents.

6. A process according to any one of preceding claims, wherein step (b) comprises the following two steps:
 - 5 i) providing a first mixture by adding one or more solvents of the second type into the solution of step (a) such that atorvastatin is still soluble, and
 - 10 ii) additionally adding one or more solvents of the second type such that atorvastatin precipitates.
7. A process according to any one of preceding claims, wherein the concentration of atorvastatin in said one or more solvents of the first type is adjusted to a range of 0.1 to 150 g/l.
- 15 8. A process according to any one of preceding claims, wherein step (a) comprises the step of concentrating the atorvastatin solution to obtain a more concentrated solution.
- 20 9. A process according to any one of preceding claims, wherein said one or more solvents of the first type comprises at least one solvent selected from the group consisting of polar or chlorinated solvents.
10. A process according to claim 9, wherein said one or more solvents of the first type comprises at least
25 one low molecular alcohol.
11. A process according to claim 10, wherein said low molecular alcohol is methanol and/or ethanol.

- 13 -

12. A process according to claim 9, wherein said polar solvent is an aprotic solvent.
13. A process according to claim 12, wherein said polar aprotic solvent is acetone.
- 5 14. A process according to any one of preceding claims, wherein said one or more solvents of the second type comprises at least one solvent selected from the group consisting of ether solvents and aliphatic solvents.
- 10 15. A process according to claim 14, wherein said solvent of the second type is diethyl ether.
- 15 16. A process according to any one of preceding claims, wherein the total amount of said solvents of the second type is at least 4 times higher than the total amount of said solvents of the first type.
17. A process according to claim 16, wherein the total amount of said solvents of the second type is 5 to 12 times higher than the total amount of said solvents of the first type.

1/2

Fig. 1

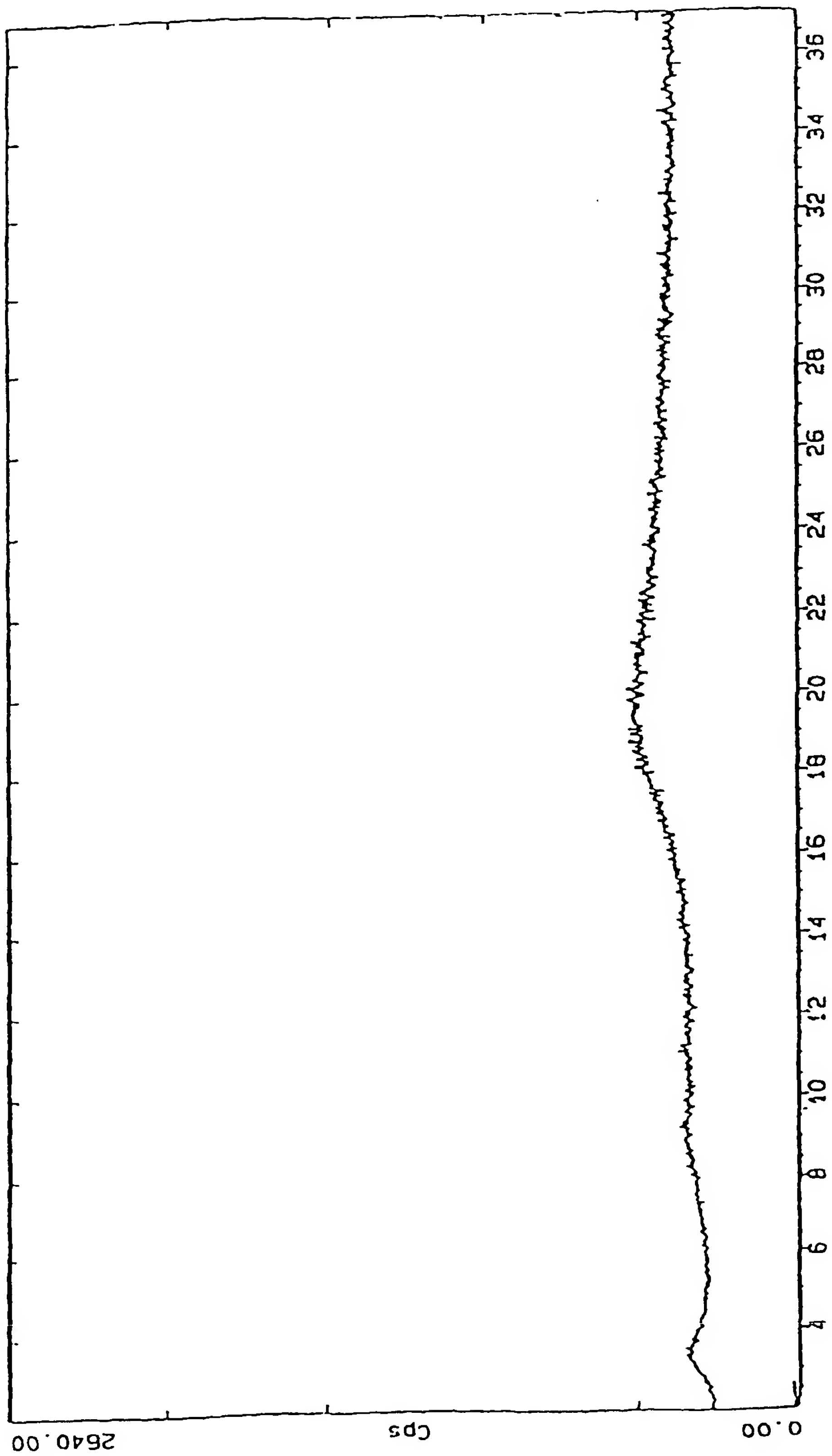
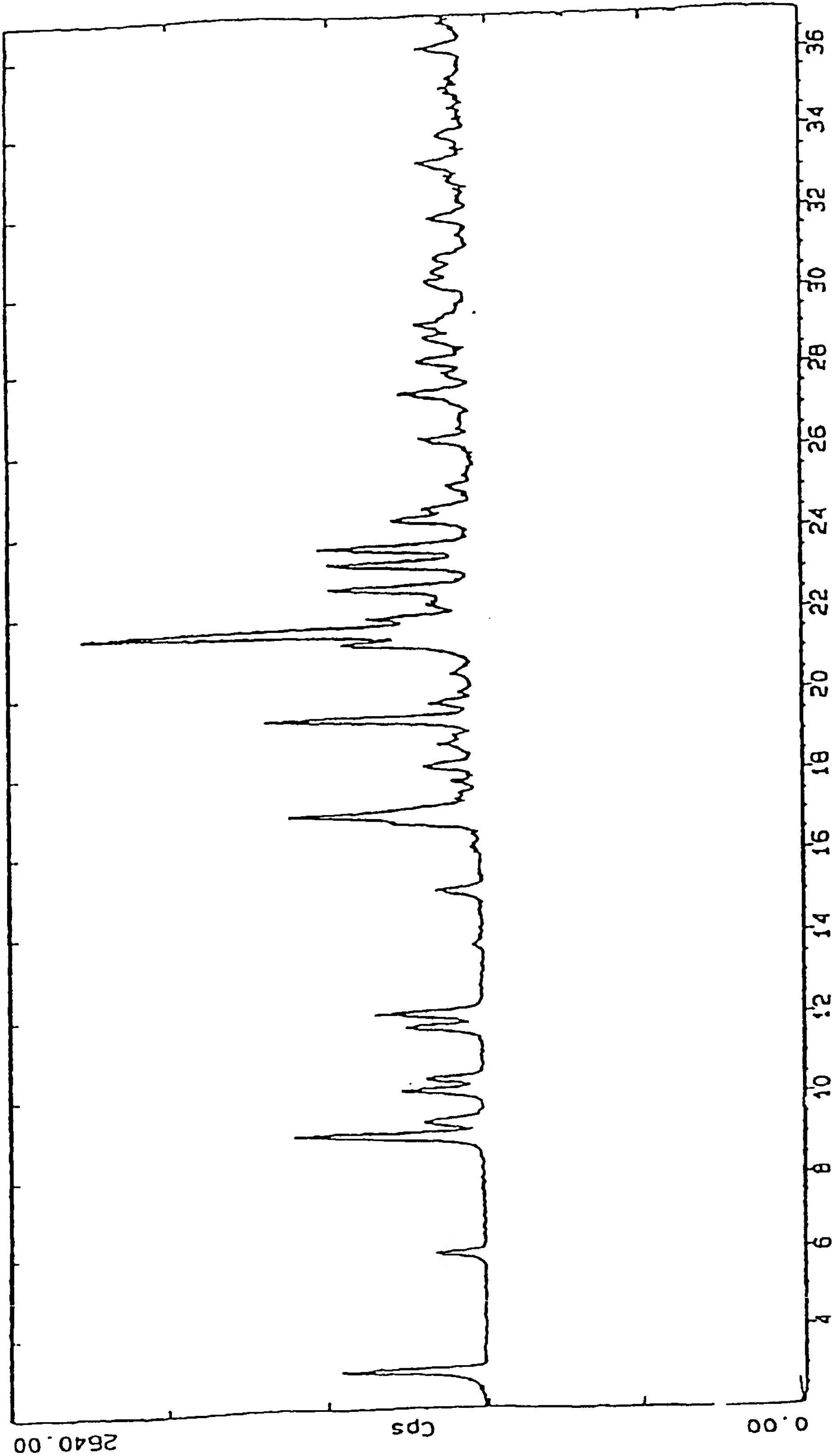


Fig.2



INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 00/01797

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/34 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 71116 A (THAPER RAJESH KUMAR ;KUMAR YATENDRA (IN); RANBAXY LAB LTD (IN); KU) 30 November 2000 (2000-11-30) page 4	1-4
A	WO 97 03960 A (WARNER LAMBERT CO ;LIN MIN (US); SCHWEISS DIETER (US)) 6 February 1997 (1997-02-06) cited in the application page 3, line 15 - line 28	1
A	US 5 385 929 A (BJORGE SUSAN M ET AL) 31 January 1995 (1995-01-31) example 2	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

24 January 2001

Date of mailing of the international search report

06/02/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk.
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Seitner, I

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/IB 00/01797

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>BAUMANN K L ET AL: "THE CONVERGENT SYNTHESIS OF CI-981, AN OPTICALLY ACTIVE, HIGHLY POTENT, TISSUE SELECTIVE INHIBITOR OF HMG-COA REDUCTASE" TETRAHEDRON LETTERS,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 33, no. 17, 21 April 1992 (1992-04-21), pages 2283-2284, XP000608147 ISSN: 0040-4039 page 2284</p> <p>---</p>	1
A	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; OISHI, SHIMAKO ET AL: "Atorvastatin (CI-981) clinical pharmacokinetic study. (I) Relative bioavailability of amorphous and crystalline preparations of atorvastatin" retrieved from STN Database accession no. 130:20148 XP002158329 abstract & YAKURI TO CHIRYO (1998), 26(8), 1241-1252 ,</p> <p>-----</p>	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 00/01797

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0071116	A	30-11-2000	NONE	
WO 9703960	A	06-02-1997	AU 700794 B	14-01-1999
			AU 6497896 A	18-02-1997
			BG 102188 A	31-08-1998
			BR 9609714 A	23-02-1999
			CA 2220455 A	06-02-1997
			CN 1190956 A	19-08-1998
			CZ 9800122 A	16-12-1998
			EP 0839132 A	06-05-1998
			HR 960312 A	28-02-1998
			IL 122161 A	14-07-1999
			JP 11510486 T	14-09-1999
			NO 980209 A	16-01-1998
			PL 324463 A	25-05-1998
			SK 5898 A	05-08-1998
US 5385929	A	31-01-1995	EP 0680963 A	08-11-1995
			JP 7304735 A	21-11-1995